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DYSLIPIDEMIA IN PATIENTS WITH RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

ROMATOİD ARTRİT VE OSTEOARTRİTLİ HASTALARDA DİSLİPİDEMİ

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SUMMARY

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease leading to disturbances of metabolism including the lipid profile.

Plasma levels of total serum cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) and very low density lipoprotein (VLDL) were comparatively measured in 30 RA, 32 osteoarthritis (OA) and 20 healthy female subjects with a mean age of 45.3 ± 11.3, 49 ± 12.0 and 46.7 ± 11.9 years respectively.

Serum TC, LDL, VLDL concentrations were found to be significantly reduced in RA patients and TC concentration was significantly higher in OA patients compared with control subjects. There was a significant correlation between the mean ESR, CRP values and TC level in RA patients. The clinical activity parameters of patients were correlated with lipid levels in RA group.

In conclusion different altered patterns of lipid and lipoproteins are observed in both RA and OA; this suggests that dyslipidemia, especially characterized by altered serum cholesterol concentration may be considered as a secondary impact of rheumatic diseases like RA and OA.

Key words : Rheumatoid arthritis, lipid, lipoprotein, osteoarthritis

ÖZET

Romatoid artrit (RA) lipid profilini de içeren metabolik bozukluklara yol açabilen kronik sistemik inflamatuar bir hastalıktır.

Yaşları sırası ile 43.5 ± 11.3, 49 ± 12.0 ve 46.7 ± 11.9 olan 30 RA'li, 32 osteoartritli (OA) ve 20 sağlıklı kadında total serum kolesterol (TC), trigliserit (TG), düşük dansiteli lipoprotein (LDL), yüksek dansiteli lipoprotein (HDL) ve çok düşük dansiteli lipoprotein (VLDL) plazma düzeyleri ölçüldü.

Kontrol grubu ile karşılaştırıldığında RA'li hastalarda serum TC, LDL, VLDL seviyeleri önemli ölçüde azalmışken, OA'li hastalarda TC seviyesi önemli ölçüde yüksek bulundu. RA'li hastalarda ortalama ESR ve CRP seviyeleri ile TC düzeyleri arasında istatistiksel olarak anlamlı bir korelasyon bulundu. RA'li grupta hastaların klinik aktivite parametreleri de lipid seviyeleri ile korele idi.

Özet olarak gerek RA'li gerekse OA'li hastalarda lipid ve lipoprotein düzeyleri özellikle de serum kolesterol düzeyleri dislipidemiye yol açacak şekilde değişmektedir. Bu RA ve OA'de hastalığın sekonder etkisine bağlanabilir.

Anahtar sözcükler : Romatoid artrit, lipit, lipoprotein, osteoartrit

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease involving the joints with an unknown pathogenesis (1). Epidemiological studies have proposed that there is an increased mortality in RA which is partly due to the atherosclerotic diseases (2,3). It is well known that low level of HDL cholesterol in the plasma is one of the most important predictors of coronary artery disease (4,5). Metabolic abnormalities and dyslipoproteinemia possibility in RA and other inflammatory rheumatic diseases have previously been described (6-8). RA patients have been found to have altered concentrations lipids and lipoprotein fractions in serum and synovial fluid characterized by a reduction in levels of all lipoprotein fractions (7,8). The results of some surveys suggest that an unknown factor closely associated with serum cholesterol may be involved in the etiology of RA or a fall in serum cholesterol concentration may predict the development of RA (9).

Here we studied fasting lipid profiles in female patients suffering from RA in comparison with age and sex matched healthy controls and patients with osteoarthritis (OA).

PATIENTS AND METHODS

30 patients with RA who had met the American College of Rheumatology criteria (10), 32 patients with degenerative

knee OA according to the definition of American Rheumatism Association (11) and 20 healthy control subjects obtained from the volunteered staff were included to the study. All the subjects were female and nonsmoking. The patients receiving oral or intraarticular steroids till 1 month before the study were not allowed. Medical history was obtained and patients with liver, kidney or thyroid abnormalities, ischemic heart disease or pregnant women were also excluded. Data about age, height, weight, disease duration, drug intake and duration of morning stiffness were obtained from the subjects. None of the subjects were taking any drug which might interfere with lipid metabolism such as ß blockers or oral contraceptives.

Hemoglobin (Hb), erythrocyte sedimentation rate (ESR), C-Reactive protein (CRP), rheumatoid factor (RF) were checked, Ritchie articular index (RAI) (12) and Health Assessment Questionnaire (HAQ) (13) were assessed as clinical activity and disability parameters in RA patients. The eight domains of HAQ measure arthritis spesific function on a scale of 0-3 where 0 represents no limitation, 3 represents most limitation. The overall HAQ score is calculated as the average of these scores and range from 0-3 (13). Hand x-rays were also performed in RA group and assessed according to the modified method of Larsen (14). The knee x-rays of OA patients were graded according to the method of Kellgren Lawrence score from 0-4 using a standard reference atlas (15).

After an overnight fasting, blood samples of the subjects were obtained and lipid profiles including the levels of total serum cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), very low density lipoprotein (VLDL) and triglyceride (TG) were measured in all subjects. Serum TC, HDL, TG were assayed by enzymatic methods, using a spectro analyser (Olympus AU 800) and Randox clinical chemistry slides were used for TC (Randox 620 CH), HDL (Randox B 700) and TG (Randox 472 TR). LDL and VLDL values were calculated using the standard formula.

Student's t test was used for comparing the variables of the groups. The relation between lipid values and the clinical and laboratory parameters were analysed using a Spearman correlation coefficient. All statistical calculation were performed using SPSS package for windows version 6.1.

RESULTS

The study included 30 RA, 32 knee OA patients and 20 healthy control subjects with a mean age of 45.3 ±11.3, 49 ± 8.1 and 46.7 ±11.9 years respectively. Although the mean age of the OA patients were higher than the other 2 groups, there was no statistical difference betweeen the mean age of the groups. The mean duration of disease was longer in OA group than in the RA group (8.9 ± 4.2 years / 6.5 ± 5.4 years). Participants with OA were more likely to be hypertensive and postmenapausal. Four patients were taking diuretics and 14 patients were receiving hormone replacement therapy in RA group while 6 patients were taking diuretics and 17 patients were taking hormone replacement therapy in OA group. There was no statistically significant difference between the groups regarding the BMI, diabetes mellitus or use of estrogen replacement therapy. The clinical and radiological variables of RA patients are listed in Table I. The mean Kellgren Lawrence score of the knee x-rays of the patients with OA was 2.75 ± 0.9.

Active disease associated with high levels of ESR and CRP was present in 13 of 30 RA patients. There were 5 patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs), 4 patients with hydroxychloroquine (HCQ)(200 mg/day) in RA group. Seventeen patients were receiving methotrexate (7.5-15 mg/weekly) and 4 patients taking salazopyrine (2g/day). In the OA group all the patients were receiving occasionally different types of NSAIDs.

Table I: The clinical variables of the patients with rheumatoid arthritis

Clinical variables	Mean ± SD
Morning stiffness (min)	86.7 ± 63.6
Hemoglobin (g/L)	13.04 ± 3.65
ESR (mm/h)	49.89 ± 26.91
CRP (mg/L)	18.25 ± 14.03
RF (IU/mL)	94.42 ± 76.69
RAI score	27.42 ± 7.11
Larsen score	19.8 ± 6.41
HAQ score	0.9 ± 0.44

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RF: Rheumatoid factor, RAI: Ritchie articular index, HAQ: Health assessment questionnaire

Dyslipidemia was detected in 21 RA, 20 OA and 7 control subjects. We compared RA patients with OA and healthy control subjects. RA patients had all lower values of TC, TG, HDL, LDL and VLDL but statistically significant reduction was existed only in TC, LDL and VLDL values when compared with healthy subjects and in TC, LDL, HDL, VLDL values when compared with OA group. In patients with active RA disease; all the levels of subsets of lipoproteins were statistically lower when compared with the other 2 groups. There was no statistically significant difference between the groups with respect to TG values. When OA patients were compared with the other groups, OA patients had statistically significant increased serum concentration of only TC compared with healthy control subjects and RA patients (Table II).

Table II: The mean values of lipid and lipoprotein concentrations (mg/dL) in patients with RA and OA

	TC	TG	LDL	HDL	VLDL
RA (n = 24)	169.2±45.2*	120.8±71.6	88±25.6*	53.5±13.6	22.5±13.1*
OA (n = 22)	236.4±49.5*	143.5±67.6	129.2±33.1	62.3±14.1	35.8±21.7
Control (n =20)	202.6±46.4	144.1±55	119.9±38.5	57.5±11.9	31.3±12.2

* $p<0.05$ (values compared with the healthy control subjects)

RA: Rheumatoid arthritis, OA: Osteoarthritis, TC: Total Cholesterol, TG: Triglycerides, LDL: Low density lipoprotein HDL: High density lipoprotein VLDL: Very low density lipoprotein

In the second part of this study we searched the correlation of lipid and lipoprotein levels with disease activity and disability parameters in RA patients and the evaluation of the results revealed a negative correlation between serum TC concentrations and ESR ($p<0.05$, $r=-0.37$) and CRP ($p<0.05$, $r=-0.39$) in RA group.

There was not a correlation between the radiological scores of OA patients and their lipid concentrations ($p>0.05$).

DISCUSSION

In this study our results indicated that the patients with RA have dyslipoproteinemia as well as the patients with OA. The abnormalities of serum lipoprotein patterns were different in these inflammatory and noninflammatory rheumatic diseases. The altered pattern were characterized by low levels of serum TC, LDL, VLDL in RA patients and increased serum concentrations of TC in OA subjects. These alterations were correlated with disease activity parameters in patients with RA confirming that activity of inflammatory disease may be an important determinant of altered lipid profile.

Dyslipoproteinemia characterized by a generalized diminution of all lipoprotein subsets have previously been described in patients with RA (6,7,16). Our observations have confirmed some of these findings but quite different in some points. Swenson et al (16) investigated lipoprotein metabolism in untreated active RA and seronegative spondyloarthropathies and suggested that RA and other inflammatory arthritis had considerable but similar abnormalities of their serum lipid pattern characterized by low TC, LDL, VLDL, HDL concentration and low TG concentrations in VLDL and HDL subfractions. Concentration of total TG in RA patients in this and other studies were similar as were concentrations in normal controls (6,7,16). However the results of some studies showed decreased concentration of total TG or triglycerides in VLDL and HDL (8). Lorber et al (6) determined lipid and lipoprotein patterns in RA patients based on the treatment that was being administered and concluded 30%, 26% and 36% reductions in TC, LDL and HDL cholesterol concentrations respectively. They also showed the absence of drug effects on altered levels of lipid profiles. The only difference demonstrated were reduced levels of VLDL and TG in the group that was treated with hydroxychloroquine. In our study the diminution in the levels of serum TC, LDL and VLDL was the result of a 15% to 25% reduction in lipoprotein subsets. This is lower than the results of other studies which were performed on untreated RA patients. Lazarevic et al (17) showed that RA patients had significantly decreased concentrations of total serum lipids TC, LDL and HDL compared with healthy subjects and this dyslipidemia was similar to that in patients with psoriatic arthritis and depended on the activity of inflammatory disease. Our results are in disagreement with the above studies (6-8,16,17) that we did not observed a statistically significant reduction in HDL values of non-active RA patients and additionally the mean level of VLDL concentration was found to be lower in our RA patients than in healthy control subjects. But we observed similar results in our active RA group. This may be due to the drug therapy administered or activity of the inflammatory disease

may play a role on these different lipoprotein levels. Previous surveys have proposed that CRP specifically binded to serum lipoproteins mainly VLDL and VLDL particules aggregated in the presence of CRP in vitro (16,18). If this condition occurs in vivo, it can explain the reduction in VLDL concentration in our RA patients who had active inflammation characterized by high values of CRP.

The altered lipoprotein pattern observed in previous studies and our study are similar with reference to reduced TC values (5-7,16,17). The correlation between TC and ESR and CRP in active RA patients raises the possibility that cholesterol behaves like an activity marker. The common points in our and previous studies are the reduction in the level of TC and similar values of TG in RA patients compared with healthy control subjects which may mean that TC can be a key point of dyslipidemia involving in the activity of chronic inflammatory diseases. According to the results of a recent epidemiologic study, the serum cholesterol concentration was thought to be directly proportional to the risk of development of RF positive RA (9). Heliovaara et al (9) suggested that an unknown factor closely associated with serum cholesterol might be involved in the etiology of RA.

The etiology of dyslipidemia in RA is not clear. The correlation of disease activity pattern and hypolipidemia imply that the degree of inflammation may play a role in the development of dyslipoproteinemia in RA patients (5,16,17). Supporting these points, hypocholesterolemia has also been described in other rheumatic inflammatory diseases like SLE and Reiter (8,17,19). The liver is a key organ in lipoprotein metabolism. The results of experimental studies indicate that in the course of inflammation, the liver preferentially uses aminoacids for the production of inflammatory mediators rather than for manufacturing the enzymes important in lipid metabolism, resulting with a reduction in production of the lipoproteins (17,20,21). Based on the results of these invivo and invitro studies, altered lipoprotein metabolism was suggested to be a systemic sequela partly due to the host's response to inflammation (16,17).

The therapy of RA may have an indirect effect on lipid metabolism (22). In previous studies it was shown that corticosteroid therapy had an increasing effect on cholesterol in HDL and decreases TG (23,24). Although NSAID may also have an effect on lipid metabolism inhibiting the production of prostoglandines which are important for normal function of gastrointestinal system (25), it has been proposed that the institution of NSAIDs on previously untreated patients did not affect the levels of lipoproteins in RA patients (26). In addition to their role as a disease modifying agent, antimalarials may have a beneficial effect on reducing hypercholesterolemia in these patients (27). In our study none of the patients were using corticosteroids or immunomodulating drugs. As the number of subjects were small in the HCQ treatment group and according to the results of Lorber et al (6) we might neglect the effect of HCQ on the lipid profile of our RA patients. But the influence of drug therapies on serum lipid and lipoprotein concentrations can not be ruled out fully in our study .

Besides dyslipidemia in patients with RA, this study showed that patients with OA had also altered levels of lipids characterized by increased concentration of TC. OA is a common joint disorder leading to a substantial disability in the older population (28). There are reports about a positive association between serum cholesterol levels and OA (28,29). Some epidemiological series concluded the independent role of serum cholesterol as a systemic risk factor for OA (30). In the Chingford study (30) hypercholesterolemia was found to be an independent risk factor for knee OA in women, the association being strongest in women with bilateral joint pathology (29). The results of our study are concurrent with the data of Baltimore longitidunal study of aging, as they have found no association between serum cholesterol levels and radiological scores of knee OA (31). Several mechanism may have role in the effect of high serum cholesterol levels on OA (28). It is likely that OA of the knee leads to a more sedantary lifestyle resulting the dimunition of physical activity that may have an additive effect on dyslipidemia (28,29). Our data provide only little information regarding the mechanism of action. Further studies are needed to confirm these findings.

In conclusion we have showed the different altered patterns of lipid and lipoproteins in both degenerative and inflammatory rheumatic diseases in comparison with healthy control subjects. Our findings may suggest that dyslipidemia observed in OA and RA is a frequent appearance and may be considered as a secondary impact of rheumatic diseases. Especially serum cholesterol concentration, as a similar factor influencing the appearance of dyslipidemia, can be considered as a risk determinant of activity in rheumatic diseases like RA and OA.

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